CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074626

Trade Name : BUTORPHANOL TARTRATE INJECTION USP

Generic Name: Butorphanol Tartrate Injection USP 1mg/ml (1ml/ml single dose vials) and 2mg/ml (1ml and 2ml single dose vials)

Sponsor : Abbott Laboratories

Approval Date: January 23, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074626

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Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074626

APPROVAL LETTER

ANDA 74-626

JAN 23 1997

Abbott Laboratories
Attention: Thomas F. Willer, Ph.D.
200 Abbott Park Road, D-389 AP30
Abbott Park, IL 60064-3537

Dear Dr. Willer:

This is in reference to your abbreviated new drug application dated February 17, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Butorphanol Tartrate Injection USP, 1 mg/mL (1 mg/mL single dose vials) and 2 mg/mL (1 mL and 2 mL single dose vials).

Reference is also made to your amendment dated September 30, 1996 and December 23, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Butorphanol Tartrate Injection USP, 1 mg/mL and 2 mg/mL vials to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Stadol® Injectable, 1 mg/mL and 2 mg/mL respectively, of Apothecon Incorporated, Division of Bristol-Myers Squibb).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

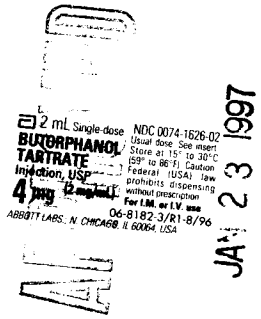
Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074626

FINAL PRINTED LABELING


2 mL Single-dose
BUTORPHANOL TARTRATE
Injection, USP
4 mg (2 mg/mL)
For I.M. or I.V. use
06-8182-3/R1-8/96
ABBOTT LABS., N. CHICAGO, IL 60064, USA
NDC 0074-1626-02
Usual dose: See insert
Store at 15° to 30°C (59° to 86°F). Caution: Federal (USA) law prohibits dispensing without prescription
JA 23 1997

APPROVED

JAN 23 1997

2 mL Single-dose Fliptop Vial **Discard unused portion.** 10 Units/**NDC 0074-1626-02**

BUTORPHANOL TARTRATE
Injection, USP
4 mg (2 mg/mL)

For I.M. or I.V. use

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

Each mL contains butorphanol tartrate 2 mg; sodium citrate, dihydrate 6.4 mg; citric acid, hydrous 3.3 mg; sodium chloride 6.4 mg.

Sterile, nonpyrogenic. Store at controlled room temperature 15° to 30°C (59° to 86°F).
Protect from light.

Caution: Federal (USA) law prohibits dispensing without prescription.

USE ASEPTIC TECHNIQUE

Remove cover from fliptop vial and cleanse stopper with antiseptic.

Usual Dosage: Adults – 2 mg I.M. (1 to 4 mg), or 1 mg I.V. (0.5 to 2 mg) every three to four hours as required.
See package insert.

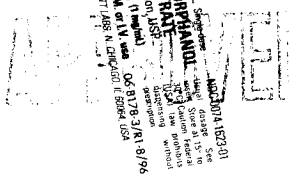
++300741626022T

08-7858-3/R1-8/96

Printed in USA

2 mL Single-dose Fliptop Vial **Discard unused portion.** 10 Units/**NDC 0074-1626-02**

BUTORPHANOL TARTRATE
Injection, USP
4 mg (2 mg/mL)
For I.M. or I.V. use
ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA


1 mL
BUTORPHANOL
TARTRATE
Injection, USP
1 mg (1 mg/mL)
For IM or IV use
NDC 0074-1623-01
See package insert for dosage information.
Store at 15° to 30°C (59° to 86°F).
Caution: Federal law prohibits dispensing without prescription
06-8178-3/R1-8/96
ABBOTT LABS, N. CHICAGO, IL 60064 USA

JAN 23 1997

1 mL Single-dose Fliptop Vial **Discard unused portion.** 10 Units/**NDC 0074-1623-01**

BUTORPHANOL TARTRATE
Injection, USP

1 mg (1 mg/mL)

For I.M. or I.V. use

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

JUL 2 3 1997

++3007416230 12P

USE ASEPTIC TECHNIQUE

Remove cover from fliptop vial and cleanse stopper with antiseptic.

Usual dosage: Adults – 2 mg I.M. (1 to 4 mg), or 1 mg I.V. (0.5 to 2 mg) every three to four hours as required.
See package insert.

1 mL Single-dose Fliptop Vial **Discard unused portion.** 10 Units/**NDC 0074-1623-01**

BUTORPHANOL TARTRATE
Injection, USP

1 mg (1 mg/mL)

For I.M. or I.V. use

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

Each mL contains butorphanol tartrate 1 mg; sodium citrate, dihydrate 6.4 mg; citric acid, hydrous 3.3 mg; sodium chloride 6.4 mg.

Sterile, nonpyrogenic. Store at controlled room temperature 15° to 30°C (59° to 86°F).
Protect from light.

Caution: Federal (USA) law prohibits dispensing without prescription.

08-7855-3/R1-8/96

Printed in USA

1 mL Single-dose

BUTORPHANOL TARTRATE

Injection, USP

2 mg (2 mg/mL)

For I.M. or I.V. use

NDC 0074-1626-01

Usual dose. See insert. Store at 15° to 30°C (59° to 86°F). Caution: Federal (USA) law prohibits dispensing without prescription

06-8181-3/R1-8/96

ABBOTT LABS., N. CHICAGO, IL 60064, USA

1 mL Single-dose Fliptop Vial **Discard unused portion.** 10 Units/**NDC 0074-1626-01**

BUTORPHANOL TARTRATE

Injection, USP

2 mg (2 mg/mL)

For I.M. or I.V. use

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

Each mL contains butorphanol tartrate 2 mg; sodium citrate, dihydrate 6.4 mg; citric acid, hydrous 3.3 mg; sodium chloride 6.4 mg.

Sterile, nonpyrogenic. Store at controlled room temperature 15° to 30°C (59° to 86°F).
Protect from light.

Caution: Federal (USA) law prohibits dispensing without prescription.

USE ASEPTIC TECHNIQUE

Remove cover from fliptop vial and cleanse stopper with antiseptic.

Usual Dosage: Adults – 2 mg I.M. (1 to 4 mg), or 1 mg I.V. (0.5 to 2 mg) every three to four hours as required.
See package insert.

++300741626012S

08-7857-3/R1-8/96

Printed in USA

1 mL Single-dose Fliptop Vial Discard unused portion. 10 Units/NDC 0074-1626-01

BUTORPHANOL TARTRATE

Injection, USP

2 mg (2 mg/mL)

For I.M. or I.V. use

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

with cool water is recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Butorphanol Tartrate Injection, USP is supplied as follows:

List No.	Container Description	Concentration (mg/mL)	Fill Volume/ Container Size	Total Butorphanol (Per Container)
1623	Single-Dose Glass Fliptop Vial	1	1 mL/2 mL	1 mg
1624	Abboject-PA Syringe	1	1 mL/2.25 mL	1 mg
1626	Single-Dose Glass Fliptop Vial	2	1 mL/2 mL	2 mg
1626	Single-Dose Glass Fliptop Vial	2	2 mL/2 mL	4 mg
1627	Abbject-PA Syringe	2	1 mL/2.25 mL	2 mg

Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light.

Caution: Federal (USA) law prohibits dispensing without prescription.

 06-9422-R1-Rev. Sept., 1996 Printed in USA
ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

BUTORPHANOL TARTRATE

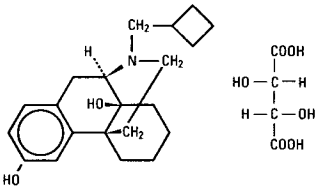
Injection, USP

Glass Fliptop Vial
Abboject®-PA Syringe

Protect from light

DESCRIPTION

Butorphanol tartrate is a synthetically derived opioid agonist-antagonist analgesic of the phenanthrene series. The chemical name is (-)-17-(cyclobutylmethyl) morphinan-3, 14-diol D-(-)- tartrate (1:1) (salt). The molecular formula is $C_{21}H_{29}NO_2,C_4H_6O_6$, which corresponds to a molecular weight of 477.55 and the following structural formula:



Butorphanol tartrate is a white powder. Its solutions are slightly acidic. It melts between 217°C and 219°C, with decomposition. It is sparingly soluble in water; slightly soluble in methanol; insoluble in alcohol and chloroform; soluble in dilute acids. The dose is expressed as the tartrate salt. One milligram of the salt is equivalent to 0.68 mg of the free base. The n-octanol/aqueous buffer partition coefficient of butorphanol is 180:1 at pH 7.5.

Butorphanol tartrate injection is a sterile, nonpyrogenic solution of butorphanol tartrate in water for injection. It is administered by intravenous or intramuscular administration.

Each milliliter (mL) contains butorphanol tartrate 1 or 2 mg; sodium citrate, dihydrate, 6.4 mg; citric acid hydrous 3.3 mg; sodium chloride 6.4 mg. The pH is 4.5 (3.0 to 5.5).

CLINICAL PHARMACOLOGY

General Pharmacology and Mechanism of Action

Butorphanol and its major metabolites are agonists at k-opioid receptors and mixed agonist-antagonists at μ-opioid receptors.

Its interactions with these receptors in the central nervous system apparently mediate most of its pharmacologic effects, including analgesia.

In addition to analgesia, CNS effects include depression of spontaneous respiratory activity and cough, stimulation of the emetic center, miosis and sedation. Effects possibly mediated by non-CNS mechanisms include alteration in cardiovascular resistance and capacitance, bronchomotor tone, gastrointestinal secretory and motor activity and bladder spincter activity.

In an animal model, the dose of the butorphanol tartrate required to antagonize morphine analgesia by 50% was similar to that for nalorphine, less than that for pentazocine and more than that for naloxone.

The pharmacological activity of butorphanol metabolites has not been studied in humans; in animal studies, butorphanol metabolites have demonstrated some analgesic activity.

In human studies of butorphanol (see CLINICAL TRIALS), sedation is commonly noted at doses of 0.5 mg or more. Narcosis is produced by 10 to 12 mg doses of butorphanol administered over 10 to 15 minutes intravenously.

Butorphanol, like other mixed agonist-antagonists with a high affinity for the kappa receptor, may produce unpleasant psychotomimetic effects in some individuals.

Nausea and/or vomiting may be produced by doses of 1 mg or more administered by any route.

In human studies involving individuals without significant respiratory dysfunction, 2 mg of butorphanol IV and 10 mg of morphine sulfate IV depressed respiration to a comparable degree. At higher doses, the magnitude of respiratory depression with butorphanol is not appreciably increased; however, the duration of respiratory depression is longer. Respiratory depression noted after administration of butorphanol to humans by any route is reversed by treatment with naloxone, a specific opioid antagonist (see Treatment in OVERDOSAGE).

Butorphanol tartrate demonstrates antitussive effects in animals at doses less than those required for analgesia.

Hemodynamic changes noted during cardiac catheterization in patients receiving single 0.025 mg/kg intravenous doses of butorphanol have included increases in pulmonary artery pressure, wedge pressure and vascular resistance, increases in left ventricular end diastolic pressure and in systemic arterial pressure.

Pharmacodynamics:

The analgesic effect of butorphanol is influenced by the route of administration. Onset of analgesia is within a few minutes for intravenous administration and within 10 to 15 minutes for intramuscular injection.

Peak analgesic activity occurs within 30 to 60 minutes following intravenous and intramuscular administration.

The duration of analgesia varies depending on the pain model as well as the route of administration, but is generally 3 to 4 hours with IM and IV doses as defined by the time

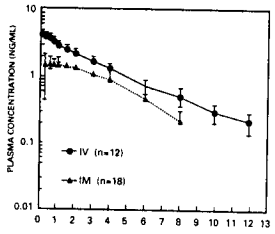
50% of patients required remedication. In postoperative studies, the duration of analgesia with IV or IM butorphanol was similar to morphine, meperidine and pentazocine when administered in the same fashion at equipotent doses (see CLINICAL TRIALS).

Pharmacokinetics:

Butorphanol Tartrate Injection, USP is rapidly absorbed after IM injection and peak plasma levels are reached in 20 to 40 minutes.

Following its initial absorption/distribution phase, the single dose pharmacokinetics of butorphanol by the intravenous and intramuscular routes of administration are similar (see Figure 1).

Figure 1—Butorphanol Plasma Levels After IV and IM Administration of 2 mg Dose



Serum protein binding is independent of concentration over the range achieved in clinical practice (up to 7 ng/mL) with a bound fraction of approximately 80%.

The volume of distribution of butorphanol varies from 305 to 901 liters and total body clearance from 52 to 154 liters/hr (see Table 1).

Table 1—Mean Pharmacokinetic Parameters of Intravenous Butorphanol in Young and Elderly Subjects[a]

Parameters	Young	Elderly
AUC (inf)[b] (hr.ng/mL)	7.24 (1.57)[d] (4.40-9.77)[e]	8.71 (2.02) (4.76-13.03)
Half-life (hr)	4.56 (1.67) (2.06-8.70)	5.61 (1.36) (3.25-8.79)

Volume of Distribution[c] (L)	487 (155) (305-901)	552 (124) (305-737)
Total body Clearance (L/hr)	99 (23) (70-154)	82 (21) (52-143)

a) Young subjects (n=24) are from 20 to 40 years old and elderly (n=24) are greater than 65 years of age.
b) Area under plasma concentration-time curve after a 1 mg dose.
c) Derived from IV data.
d) Mean (1 S.D.)
e) (range of observed values)

The drug is transported across the blood-brain and placental barriers and into human milk (see Labor and Delivery and Nursing Mothers under PRECAUTIONS).

Butorphanol is extensively metabolized in the liver. Metabolism is qualitatively and quantitatively similar following intravenous or intramuscular administration. Oral bioavailability is only 5 to 17% because of extensive first pass metabolism of butorphanol.

The major metabolite of butorphanol is hydroxybutorphanol, while norbutorphanol is produced in small amounts. Both have been detected in plasma following administration of butorphanol. Preliminary evidence suggests the elimination half-life of hydroxybutorphanol may be greater than that of its parent.

Elimination occurs by urine and fecal excretion. When ^{3}H labeled butorphanol is administered to normal subjects, most (70 to 80%) of the dose is recovered in the urine, while approximately 15% is recovered in the feces.

About 5% of the dose is recovered in the urine as butorphanol. Forty-nine percent is eliminated in the urine as hydroxybutorphanol. Less than 5% is excreted in the urine as norbutorphanol (see also CLINICAL PHARMACOLOGY above).

Pharmacokinetics in the elderly differ from younger patients (see Table 1).

In renally impaired patients with creatinine clearances < 30 mL/min the elimination half-life is approximately doubled and the total body clearance is approximately one half (10.5 hours [clearance 150 L/h] as compared to 5.8 hours [clearance 260 L/h] in normals). No effect was observed on C_{max} or T_{max} after a single dose.

For further recommendations refer to statements on use in Geriatric Patients, Renal Disease, Hepatic Disease, and statement on Drug Interactions in the PRECAUTIONS section, and Individualization of Dosage below.

Clinical Trials

The effectiveness of opioid analgesics varies in different pain syndromes. Studies with Butorphanol tartrate Injection, have been performed in postoperative (primarily abdominal and orthopedic) pain and pain during labor and delivery, as preoperative and preanesthetic medication, and as a supplement to balanced anesthesia (see below).

Postoperative Analgesia

The analgesic efficacy of butorphanol tartrate injection in postoperative pain was investigated in several double-blind active-controlled studies involving 958 butorphanol-treated patients. The following doses were found to have

approximately equivalent analgesic effect: 2 mg butorphanol, 10 mg morphine, 40 mg pentazocine and 80 mg meperidine.

After intravenous administration of butorphanol tartrate onset and peak analgesic effect occurred by the time of first observation (30 minutes). After intramuscular administration, pain relief onset occurred at 30 minutes or less, and peak effect occurred between 30 minutes and one hour. The duration of action of butorphanol tartrate injection was 3 to 4 hours when defined as the time necessary for pain intensity to return to pretreatment level or the time to retreatment.

Preanesthetic Medication

Butorphanol tartrate injection, (2 mg and 4 mg) and meperidine (80 mg) were studied for use as preanesthetic medication in hospitalized surgical patients. Patients received a single intramuscular dose of either butorphanol or meperidine approximately 90 minutes prior to anesthesia. The anesthesia regimen included barbiturate induction, followed by nitrous oxide and oxygen with halothane or enflurane, with or without a muscle relaxant.

Anesthetic preparation was rated as satisfactory in all 42 butorphanol injection patients regardless of the type of surgery.

Balanced Anesthesia

Butorphanol tartrate administered intravenously (mean dose 2 mg) was compared to intravenous morphine sulfate (mean dose 10 mg) as premedication shortly before thiopental induction, followed by balanced anesthesia in 50 ASA Class 1 and 2 patients. Anesthesia was then maintained by repeated intravenous doses, averaging 4.6 mg butorphanol and 22.8 mg morphine per patient.

Anesthetic induction and maintenance were generally rated as satisfactory with both butorphanol injection (25 patients) and morphine (25 patients) regardless of the type of surgery performed. Emergence from anesthesia was comparable with both agents.

Labor (see PRECAUTIONS)

The analgesic efficacy of intravenous butorphanol tartrate injection was studied in pain during labor. In a total of 145 patients butorphanol (1 mg and 2 mg) was as effective as 40 mg and 80 mg of meperidine (144 patients) in the relief of pain in labor with no effect on the duration or progress of labor. Both drugs readily crossed the placenta and entered fetal circulation. The condition of the infants in these studies, determined by Apgar scores at 1 and 5 minutes (8 or above) and time to sustained respiration showed that butorphanol had the same effects on the infants as meperidine.

In these studies neurobehavioral testing in infants exposed to butorphanol injection at a mean of 18.6 hours after delivery, showed no significant differences between treatment groups.

Individualization of Dosage

The usual starting doses of butorphanol tartrate injection are: 1 mg repeated every 3 to 4 hours IV or 2 mg repeated every 3 to 4 hours IM (see DOSAGE AND ADMINISTRATION).

Use of butorphanol in geriatric patients, patients with renal impairment, patients with hepatic impairment, and during labor requires extra caution (see below and the appropriate sections in PRECAUTIONS).

For pain relief the recommended initial dosage regimen of butorphanol tartrate injection is 1 mg IV or 2 mg IM with repeated doses every three to four hours as necessary. This dosage regimen is likely to be effective for the majority of patients. Dosage adjustments of butorphanol injection should be based on observations of its beneficial and adverse effects. The initial dose in the elderly and in patients with renal or hepatic impairment should generally be half the recommended adult dose (0.5 mg IV and 1 mg IM). Repeat doses in these patients should be determined by the patient's response rather than at fixed intervals but will generally be no less than 6 hours (see PRECAUTIONS).

The usual preoperative dose is 2 mg IM given 60 to 90 minutes before surgery or 2 mg IV shortly before induction. This is approximately equivalent in sedative effect to 10 mg morphine or 80 mg of meperidine. This single preoperative dose should be individualized based on age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used and the surgical procedure involved.

During maintenance in balanced anesthesia the usual incremental dose of butorphanol tartrate is 0.5 to 1.mg IV. The incremental dose may be higher, up to 0.06 mg/kg (4 mg/70 kg), depending on previous sedative, analgesic, and hypnotic drugs administered. The total dose of butorphanol injection will vary; however, patients seldom require less than 4 mg or more than 12.5 mg (approximately 0.06 to 0.18 mg/kg).

As with other opioids of this class, butorphanol injection may not provide adequate intraoperative analgesia in every patient or under all conditions. A failure to achieve successful analgesia during balanced anesthesia is commonly reflected by increases in general sympathetic tone. Consequently, if blood pressure or heart rate continue to rise, consideration should be given to adding a potent volatile liquid inhalation anesthetic or another intravenous medication.

In labor, the recommended initial dose of butorphanol tartrate is 1 or 2 mg IM or IV in mothers with fetuses of 37 weeks gestation or beyond and without signs of fetal distress. Dosage adjustments of butorphanol in labor should be based on initial response with consideration given to concomitant analgesic or sedative drugs and the expected time of delivery. A dose should not be repeated in less than four hours nor administered less than four hours prior to the anticipated delivery (see PRECAUTIONS).

INDICATIONS AND USAGE

Butorphanol tartrate injection, is indicated for the management of pain when the use of an opioid analgesic is appropriate.

Butorphanol tartrate injection is also indicated as a preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of pain during labor.

CONTRAINDICATIONS

Butorphanol tartrate injection is contraindicated in patients hypersensitive to butorphanol tartrate.

WARNINGS

Patients Dependent on Narcotics

Because of its opioid antagonist properties, butorphanol is not recommended for use in

patients dependent on narcotics. Such patients should have an adequate period of withdrawal from opioid drugs prior to beginning butorphanol therapy. In patients taking opioid analgesics chronically, butorphanol has precipitated withdrawal symptoms such as anxiety, agitation, mood changes, hallucinations, dysphoria, weakness and diarrhea.

Because of the difficulty in assessing opioid tolerance in patients who have recently received repeated doses of narcotic analgesic medication, caution should be used in the administration of butorphanol to such patients.

PRECAUTIONS

Head Injury and Increased Intracranial Pressure

As with other opioids, the use of butorphanol in patients with head injury may be associated with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, drug-induced miosis, and alterations in mental state that would obscure the interpretation of the clinical course of patients with head injuries. In such patients, butorphanol should be used only if the benefits of use outweigh the potential risks.

Disorders of Respiratory Function or Control

Butorphanol may produce respiratory depression, especially in patients receiving other CNS active agents, or patients suffering from CNS diseases or respiratory impairment.

Hepatic and Renal Disease

In patients with severe hepatic or renal disease the initial dosage interval for Butorphanol Tartrate Injection, USP should be increased to 6 to 8 hours until the response has been well characterized. Subsequent doses should be determined by patient response rather than being scheduled at fixed intervals (see Individualization of Dosage).

Cardiovascular Effects

Because butorphanol may increase the work of the heart, especially the pulmonary circuit (see CLINICAL PHARMACOLOGY), the use of butorphanol in patients with acute myocardial infarction, ventricular dysfunction, or coronary insufficiency should be limited to those situations where the benefits clearly outweigh the risk.

Severe hypertension has been reported rarely during butorphanol therapy. In such cases, butorphanol should be discontinued and the hypertension treated with antihypertensive drugs. In patients who are not opioid dependent, naloxone has also been reported to be effective.

Information for Patients

1. Drowsiness and dizziness related to the use of butorphanol may impair mental and/or physical abilities required for the performance of potentially hazardous tasks (e.g., driving, operating machinery, etc).
2. Alcohol should not be consumed while using butorphanol. Concurrent use of butorphanol with drugs that affect the central nervous system (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects such as drowsiness, dizziness and impaired mental function.

Drug Interactions

Concurrent use of butorphanol with central nervous system depressants (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects. When used concurrently with such drugs, the dose of

butorphanol should be the smallest effective dose and the frequency of dosing reduced as much as possible when administered concomitantly with drugs that potentiate the action of opioids.

It is not known if the effects of butorphanol are altered by concomitant medications that affect hepatic metabolism of drugs (cimetidine, erythromycin, theophylline, etc.), but physicians should be alert to the possibility that a smaller initial dose and longer intervals between doses may be needed.

No information is available about the use of butorphanol concurrently with MAO inhibitors.

Use in Ambulatory Patients

Drowsiness and dizziness related to the use of butorphanol may impair mental and/or physical abilities required for the performance of potentially hazardous tasks (e.g., driving, operating machinery, etc.). Patients should be told to use caution in such activities until their individual responses to butorphanol have been well characterized.

Alcohol should not be consumed while using butorphanol. Concurrent use of butorphanol with central nervous system depressants (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of butorphanol has not been adequately evaluated.

Butorphanol was not genotoxic in *S. typhimurium* or *E. coli* assays or in unscheduled DNA synthesis and repair assays conducted in cultured human fibroblast cells.

Rats treated orally with 160 mg/kg/day (944 mg/m^2) had a reduced pregnancy rate. However, a similar effect was not observed with a 2.5 mg/kg/day (14.75 mg/m^2) subcutaneous dose.

Pregnancy

Pregnancy Category C

Reproduction studies in mice, rats and rabbits during organogenesis did not reveal any teratogenic potential to butorphanol. However, pregnant rats treated subcutaneously with butorphanol at 1 mg/kg (5.9 mg/m^2) had a higher frequency of stillbirths than controls. Butorphanol at 30 mg/kg/oral (5.1 mg/m^2) and 60 mg/kg/oral (10.2 mg/m^2) also showed higher incidences of post-implantation loss in rabbits.

There are no adequate and well-controlled studies of butorphanol in pregnant women before 37 weeks of gestation. Butorphanol tartrate injection should be used during pregnancy only if the potential benefit justifies the potential risk to the infant.

Labor and Delivery

Although there have been rare reports of infant respiratory distress/apnea following the administration of Butorphanol tartrate during labor, this adverse effect was not attributed to butorphanol as used during controlled clinical trials. The reports of respiratory distress/apnea have been associated with administration of a dose within two hours of delivery, use of multiple doses, use with additional analgesic or sedative drugs, or use in preterm pregnancies.

In a study of 119 patients, the administration of 1 mg of IV butorphanol injection during labor was associated with transient (10 to 90 minutes) sinusoidal fetal heart rate patterns, but was not associated with adverse neonatal outcomes. In the presence of

an abnormal fetal heart rate pattern, butorphanol injection should be used with caution.

Nursing Mothers

Butorphanol has been detected in milk following administration of butorphanol tartrate injection to nursing mothers. The amount an infant would receive is probably clinically insignificant (estimated 4 microgram/liter of milk in a mother receiving 2 mg IM four times a day).

Pediatric Use

Butorphanol is not recommended for use in patients below 18 years of age because safety and efficacy have not been established in this population.

Geriatric Use

The initial dose of butorphanol recommended for elderly patients is half the usual dose at twice the usual interval. Subsequent doses and intervals should be based on the patient response (see Individualization of Dosage).

Due to changes in clearance, the mean half-life of butorphanol is increased by 25% (to over 6 hours) in patients over the age of 65. Elderly patients may be more sensitive to its side effects.

ADVERSE REACTIONS

A total of 2446 patients were studied in butorphanol clinical trials. Approximately half received butorphanol tartrate injection with the remainder receiving butorphanol tartrate nasal spray. In nearly all cases the type and incidence of side effects with butorphanol by any route were those commonly observed with opioid analgesics.

The adverse experiences described below are based on data from short- and long-term clinical trials in patients receiving butorphanol by any route and from post-marketing experience with butorphanol tartrate injection. There has been no attempt to correct for placebo effect or to subtract the frequencies reported by placebo treated patients in controlled trials.

The most frequently reported adverse experiences across all clinical trials with butorphanol tartrate injection and nasal spray were somnolence (43%), dizziness (19%), nausea and/or vomiting (13%). In long-term trials with nasal butorphanol only, nasal congestion (13%) and insomnia (11%) were frequently reported.

The following adverse experiences were reported at a frequency of 1% or greater, and were considered to be probably related to the use of butorphanol:

Body as Whole: asthenia/lethargy*, headache*, sensation of heat
Cardiovascular: VASODILATION*, PALPITATIONS
Digestive: ANOREXIA*, CONSTIPATION*. dry mouth*, nausea and/or vomiting (13%), stomach pain
Nervous: anxiety, confusion*, dizziness (19%), euphoria, floating feeling, INSOMNIA (11%), nervousness, paresthesia, somnolence (43%), TREMOR
Respiratory: BRONCHITIS. COUGH, DYSPNEA*, EPISTAXIS*, NASAL CONGESTION (13%), NASAL IRRITATION*, PHARYNGITIS*, RHINITIS*, SINUS CONGESTION*, SINUSITIS, UPPER RESPIRATORY INFECTION*
Skin and Appendages: sweating/clammy*, pruritus
Special Senses: blurred vision, EAR PAIN, TINNITUS*, UNPLEASANT TASTE* (also seen in short-term trials with butorphanol tartrate nasal spray).

(Reactions occurring with a frequency of 3 to 9% are marked with an asterisk*.

Reactions reported predominantly from long-term trials with nasally administered butorphanol tartrate are CAPITALIZED.)

The following adverse experiences were reported with a frequency of less than 1%, of the patients studied in short term butorphanol tartrate nasal spray trials and were considered to be probably related to the use of butorphanol.

Cardiovascular: hypotension, syncope
Nervous: abnormal dreams, agitation, *drug dependence,* dysphoria, hallucinations, hostility
Skin and Appendages: rash/hives
Urogenital: impaired urination

(Reactions reported only from post-marketing experience are *italicized.*)

The following infrequent additional adverse experiences were reported in a frequency of less than 1% of the patients studied in short-term butorphanol tartrate nasal spray trials and from post-marketing experiences under circumstances where the association between these events and butorphanol administration is unknown. They are being listed as alerting information for the physician.

Body as Whole: edema
Cardiovascular: hypertension
Nervous: *convulsion, delusion,* depression
Respiratory: *apnea,* shallow breathing

(Reactions reported only from post-marketing experience are *italicized.*)

DRUG ABUSE AND DEPENDENCE

Although the mixed agonist-antagonist opioid analgesics, as a class, have lower abuse potential than morphine, all such drugs can be and have been reported to be abused.

Chronic use of butorphanol tartrate injection has been reported to result in mild withdrawal syndromes, and reports of overuse and self-reported addiction have been received.

Special care should be exercised in administering butorphanol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is necessary, such patients should be closely supervised.

OVERDOSAGE

Clinical Manifestations

The clinical manifestations of overdose are those of opioid drugs, the most serious of which are hypoventilation, cardiovascular insufficiency and/or coma.

Overdose can occur due to accidental or intentional misuse of butorphanol, especially in young children who may gain access to the drug in the home.

Treatment

The management of suspected butorphanol overdosage includes maintenance of adequate ventilation, peripheral perfusion, normal body temperature, and protection of the airway. Patients should be under continuous observation with adequate serial measures of mental state, responsiveness and vital signs. Oxygen and ventilatory assistance should be available with continual monitoring by pulse oximetry if indicated. In the presence of coma, placement of an artificial airway may be required. An adequate intravenous portal should be maintained to facilitate treatment of hypotension

5

associated with vasodilation.

The use of a specific opioid antagonist such as naloxone should be considered. As the duration of butorphanol action usually exceeds the duration of action of naloxone, repeated dosing with naloxone may be required.

DOSAGE AND ADMINISTRATION

Factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and surgical procedure involved. Use in the elderly, patients with hepatic or renal disease or in labor requires extra caution (see PRECAUTIONS and CLINICAL PHARMACOLOGY, Individualization of Dosage). The following doses are for patients who do not have impaired hepatic or renal function and who are not on CNS active agents.

Use for Pain

Intravenous: The usual recommended single dose for IV administration is 1 mg repeated every three to four hours as necessary. The effective dosage range, depending on the severity of pain, is 0.5 to 2 mg repeated every three to four hours.

Intramuscular: The usual recommended single dose for IM administration is 2 mg in patients who will be able to remain recumbent, in the event drowsiness or dizziness occurs. This may be repeated every three to four hours, as necessary. The effective dosage range depending on the severity of pain is 1 to 4 mg repeated every three to four hours. There are insufficient clinical data to recommend single doses above 4 mg.

Use as Preoperative/Preanesthetic Medication

The preoperative medication dosage of butorphanol should be individualized (see CLINICAL PHARMACOLOGY, Individualization of Dosage). The usual adult dose is 2 mg IM, administered 60 to 90 minutes before surgery. This is approximately equivalent in sedative effect to 10 mg morphine or 80 mg meperidine.

Use in Balanced Anesthesia

The usual dose of Butorphanol tartrate injection is 2 mg IV shortly before induction and/or 0.5 to 1 mg IV in increments during anesthesia. The increment may be higher, up to 0.06 mg/kg (4 mg/70 kg), depending on previous sedative, analgesic, and hypnotic drugs administered. The total dose of butorphanol injection will vary; however, patients seldom require less than 4 mg or more than 12.5 mg (approximately 0.06 to 0.18 mg/kg).

Labor

In patients at full term in early labor a 1 to 2 mg dose of butorphanol tartrate IV or IM may be administered and repeated after 4 hours. Alternative analgesia should be used for pain associated with delivery or if delivery is expected to occur within 4 hours .

If concomitant use of butorphanol with drugs that may potentiate its effects is deemed necessary (see Drug Interactions in PRECAUTION SECTION) the lowest effective dose should be employed.

Safety and Handling

Butorphanol tartrate injection is supplied in sealed delivery systems that have a low risk of accidental exposure to health care workers. Ordinary care should be taken to avoid aerosol generation while preparing a syringe for use. Following skin contact, rinsing with cool water is recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Butorphanol Tartrate Injection, USP is supplied as follows:

List No.	Container Description	Concentration (mg/mL)	Fill Volume/ Container Size	Total Butorphanol (Per Container)
1623	Single-Dose Glass Fliptop Vial	1	1 mL/2 mL	1 mg
1624	Abboject-PA Syringe	1	1 mL/2.25 mL	1 mg
1625	Single-Dose Glass Fliptop Vial	2	1 mL/2 mL	2 mg
1626	Single-Dose Glass Fliptop Vial	2	2 mL/2 mL	4 mg
1626	Single-Dose Glass Fliptop Vial	2	1 mL/2.25 mL	2 mg
1627	Abboject-PA Syringe	2	1 mL/2.25 mL	2 mg

Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light.

Caution: Federal (USA) law prohibits dispensing without prescription.

06-9422-R1-Rev. Sept., 1996 Printed in USA
ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074626

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO.3

2. ANDA # 74-626

3. NAME AND ADDRESS OF APPLICANT
Abbott Laboratories
Attention: Dr. Thomas F. Willer
200 Abbott Park Road, D-389 AP30
Abbot Park, IL 60064-3537

4. LEGAL BASIS FOR SUBMISSION
Stadol-Bristol-Myers Squibb Co.
No applicable patent or exclusivity periods for injectable form. Patent for nasal administration only and expired 12/94.

5. SUPPLEMENT(s)
NA

6. PROPRIETARY NAME
NA

7. NONPROPRIETARY NAME
Butorphanol Tartrate Injection, USP.

8. SUPPLEMENT(s) PROVIDE(s) FOR:
NA

9. AMENDMENTS AND OTHER DATES:
Firm:
February 17, 1995: Original submission
March 21, 1995: Amendment
February 9, 1996: Amendment
September 30, 1996: Minor amendment

FDA:
August 22, 1995: Deficiency letter
August 5, 1996: Minor amendment

10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesic

11. Rx or OTC
Rx

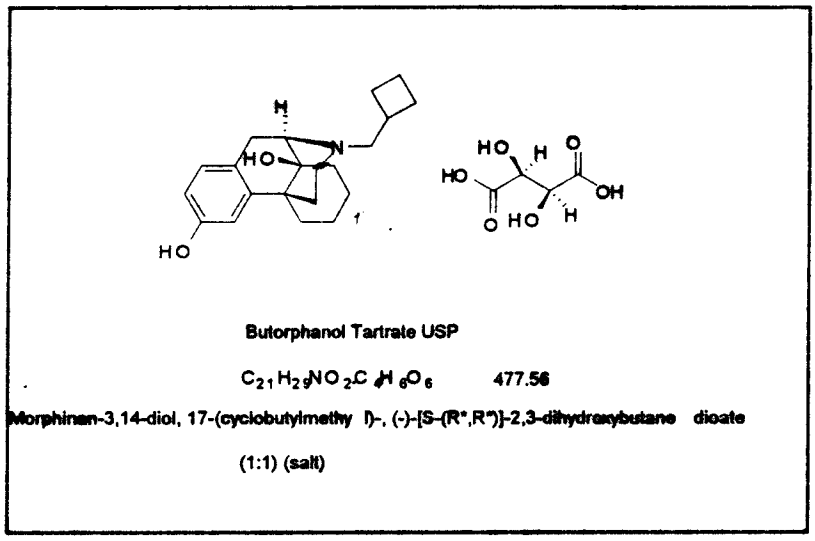
12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

13. DOSAGE FORM
Injection (1 mg/mL, 1 ml single dose vial)(2 mg/mL, 1 ml and 2 ml single Dose Vial.)

14. POTENCIES
1 mg/ml and 2 mg/ml

15. CHEMICAL NAME AND STRUCTURE
Morphinan-3,14-diol, 17-(cyclobutylmethyl)-,(-), [S-(R*, R*)]-2,3-dihydroxybutanedionate (1:1)(salt).
(-)-17-(cycobutylmethyl)morphinan-3,14-diol D-(-)-tartrate(1:1)(salt).



16. RECORDS AND REPORTS
Telephone conversation between firm and Harvey Greenberg (2-27-95), regarding five Butorphanol Tartrate Injections that should of been compressed into three applications.

17. COMMENTS
The following deficiencies are found in the review.
-EER pending

18. CONCLUSIONS AND RECOMMENDATIONS
This application can be approved based on receipt of acceptable EER. The approval letter will be issued.

19. REVIEWER: DATE COMPLETED:
Sema Basaran, Ph.D. 10-16-96 /10-25-96(labeling)
11-6-96 (DMF)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074626

BIOEQUIVALENCE REVIEW(S)

9.V

ANDA 74-626

DEC 22 1995

Abbott Laboratories
Attention: Frederick A. Gustafson
One Abbott Park Road
Abbot Park IL 60064

Dear Sir:

Reference is made to your abbreviated new drug application dated February 17, 1995, submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Butorphanol Tartrate injection USP, 1 mg/mL and 2 mg/mL vials.

The following comments pertain **only** to bioequivalency issues in the February 17, and March 21, 1995 submissions.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-626 SPONSOR: Abbott Lab
DRUG: Butorphanol Tartrate
DOSAGE FORM: Injection
STRENGTH(s): 2 mg/mL, 1 & 2 mL vials
TYPE OF STUDY: Single/Multiple Fasting/Fed
STUDY SITE: N/A

STUDY SUMMARY: The waiver of *in vivo* bioequivalence study requirements for the test product 2 mg/mL, 1 and 2 mL vials is granted

DISSOLUTION: N/A

PRIMARY REVIEWER: /S/ BRANCH: III
INITIAL: /S/ DATE: 12/21/95

BRANCH CHIEF: BRANCH:
INITIAL: /S/ DATE: 12/21/95

DIRECTOR
DIVISION OF BIOEQUIVALENCE
INITIAL: /S/ DATE: 12/21/95

DIRECTOR
OFFICE OF GENERIC DRUGS Not first generic
INITIAL: N/A DATE:

AUG 31 1995

Butorphanol Tartrate Injection
1 mg/mL, 1 mL Vial
ANDA # 74-626
Reviewer: Moheb H. Makary
WP 74626W.295

Abbott Laboratories
Abbott Park, Illinois
Submission Date:
February 17, 1995

Review of a Waiver request

I. Objective:

The firm has requested a waiver of bioavailability test requirements for its Butorphanol Tartrate Injection, USP, 1 mg/mL, 1 mL Vial. The test product is for intravenous or intramuscular use. The firm submitted the formulations of the test product and corresponding reference product (Stadol® injection 1 mg/mL, Apothecon, Bristol-Myers Squibb).

II. Background:

Butorphanol tartrate, sterile, parenteral, narcotic analgesic agent with agonist-antagonist activity, is a member of phenanthrene series. The duration of analgesia is generally 3 to 4 hours and is approximately equivalent to that of morphine. The onset time for analgesia is within 10 minutes following intramuscular injection and very rapidly following intravenous administration. Peak analgesic activity is obtained at 30 to 60 minutes following intramuscular injection and more rapidly following intravenous injection.

III. Formulations:

The formulations of the test and reference products are shown below:

	Apothecon Bristol-Myers Squibb	Abbott Laboratories
	Stadol® (Butorphanol Tartrate Injection, USP)	Butorphanol Tartrate Injection, USP
Ingredients	**mg/mL**	**mg/mL**
Butorphanol Tartrate, USP	1.0	1.0
Sodium Citrate Dihydrate, USP	6.4	6.4
Anhydrous Citric Acid, USP	3.3	3.0
Sodium Chloride, USP	6.4	6.4
Water for Injection, USP	q.s.	q.s.
Nitrogen	----	q.s.

IV. Comments:

1.The formulation of Abbott's test product (Butorphanol Tartrate, Injection, USP, 1 mg/mL, 1 mL Vial), is identical to the formulation of Bristol's reference product (Stadol® Injection, 1 mg/mL) except the formulation of the test product contains 3.0 mg/mL of anhydrous citric acid, whereas the reference product formulation contains 3.3 mg/mL.

2. The difference in the citric acid concentration for the test and reference products is within the acceptable range of 0.01-0.8% for that route of administration as reported in the Inactive Ingredient Guide (IIG, October 1993).

3. The difference in concentration of citric acid (buffer) between the test and reference products (3.0 mg/mL vs. 3.3 mg/mL) should not affect the safety of the proposed test product since the labeling of the test product stated that the pH is 4.5 (3.0 to 5.5). This pH is acceptable for an aqueous solution of USP Butorphanol Tartrate for Injection (USP 23, page 241).

V. Recommendation:

The Division of Bioequivalence agrees that the information submitted by Abbott Laboratories, demonstrates that Butorphanol Tartrate Injection, USP, 1 mg/mL, 1 mL Vial, falls under 21 CFR 320.22 (e) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study requirements for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation to be bioequivalence to Stadol® (butorphanol tartrate) Injectable, 1 mg/mL, manufactured by Apothecon, Bristol-Myers Squibb.

The firm should be informed of the above recommendation.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE /S/
FT INITIALLED RMHATRE

Date: 8/22/95

/S/

Concur: _____ Date: 8/31/95

Keith Chan, Ph.D.
Director
Division of Bioequivalence

MMakary:8-16-95 wp 74626W.295

DEC 7 1995 9,J

Butorphanol Tartrate Injection
2 mg/mL, 1 & 2 mL Vials
ANDA # 74-626
Reviewer: Moheb H. Makary
WP 74626W.395

Abbott Laboratories
Abbott Park, Illinois
Submission Date:
March 21, 1995

Review of a Waiver request

I. Objective:

The firm has requested a waiver of bioavailability test requirements for its Butorphanol Tartrate Injection, USP, 2 mg/mL, 1 & 2 mL Vials. The test product is for intravenous or intramuscular use. The firm submitted the formulations of the test product and corresponding reference product (Stadol® injection 2 mg/mL, 1 & 2 mL Vials, Apothecon, Bristol-Myers Squibb).

On February 17, 1995, the firm requested a waiver of in vivo bioequivalence study requirements for its Butorphanol Tartrate Injection, 1 mg/mL, 1 mL Vial. Waiver was granted on August 31, 1995 (ANDA #74-626 submission dated February 17, 1995).

II. Background:

Butorphanol tartrate, sterile, parenteral, narcotic analgesic agent with agonist-antagonist activity, is a member of phenanthrene series. The duration of analgesia is generally 3 to 4 hours and is approximately equivalent to that of morphine. The onset time for analgesia is within 10 minutes following intramuscular injection and very rapidly following intravenous administration. Peak analgesic activity is obtained at 30 to 60 minutes following intramuscular injection and more rapidly following intravenous injection.

III. Formulations:

The formulations of the test and reference products are shown below:

	Apothecon Bristol-Myers Squibb	Abbott Laboratories
	Stadol® (Butorphanol Tartrate Injection, USP)	Butorphanol Tartrate Injection, USP
Ingredients	**mg/mL**	**mg/mL**
Butorphanol Tartrate, USP	2.0	2.0
Sodium Citrate Dihydrate, USP	6.4	6.4
Anhydrous Citric Acid, USP	3.3	3.0

Sodium Chloride, USP	6.4	6.4
Water for Injection, USP	q.s.	q.s.
Nitrogen	----	q.s.

IV. Comments:

1.The formulation of Abbott's test product (Butorphanol Tartrate, Injection, USP, 2 mg/mL, 1 & 2 mL Vials), is identical to the formulation of Bristol's reference product (Stadol® Injection, 2 mg/mL) except the formulation of the test product contains 3.0 mg/mL of anhydrous citric acid, whereas the reference product formulation contains 3.3 mg/mL.

2. The difference in the citric acid concentration for the test and reference products is within the acceptable range of 0.01-0.8% for that route of administration as reported in the Inactive Ingredient Guide (IIG, October 1993).

3. The difference in concentration of citric acid (buffer) between the test and reference products (3.0 mg/mL vs. 3.3 mg/mL) should not affect the safety of the proposed test product since the labeling of the test product stated that the pH is 4.5 (3.0 to 5.5). This pH is acceptable for an aqueous solution of USP Butorphanol Tartrate for Injection (USP 23, page 241).

V. Recommendation:

The Division of Bioequivalence agrees that the information submitted by Abbott Laboratories, demonstrates that Butorphanol Tartrate Injection, USP, 2 mg/mL, 1 & 2 mL Vials, falls under 21 CFR 320.22 (e) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study requirements for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation to be bioequivalence to Stadol® (butorphanol tartrate) Injectable, 2 mg/mL, 1 & 2 mL Vials, manufactured by Apothecon, Bristol-Myers Squibb.

The firm should be informed of the above recommendation.

/S/

Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE /S/
FT INITIALLED RMHATRE Date: 11/20/95